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Attenuation of Increased Regional Myocardial Oxygen Consumption During Exercise As a Major Cause of Warm-Up Phenomenon

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Objectives. **The aim of this study was to test the hypothesis that the warm-up phenomenon is attributable to a reduction of increased myocardial oxygen consumption rather than to increased coronary blood flow during exercise.**

Background. **The underlying mechanism of the warm-up phenomenon is not elucidated.**

Methods. **Thirteen patients with effort angina were subjected to two consecutive supine ergometer exercise tests performed 15 min apart. All patients had severe proximal stenosis (>90%) in the left anterior descending coronary artery. Great cardiac vein flow was measured before and during exercise. Both regional myocardial oxygen consumption and adenosine release were determined.**

Results. **Exercise was continued for significantly longer before angina onset in the second than in the first exercise test (507 ± 44 vs. 410 ± 42 s, $p < 0.01$). The extent of ST segment depression in lead V_5 of the electrocardiogram (ECG) was larger at the time of angina onset in the first (1.7 ± 0.2 mm) than in the second (1.1 ± 0.2 mm, $p < 0.01$) exercise test. Neither systemic hemodynamic variables nor great cardiac vein flow differed between the first and second exercise tests. In contrast, regional myocardial oxygen consumption assessed at 3 min of exercise was significantly ($p < 0.01$) less in the second than in the first test (8.0 ± 0.8 vs. 8.7 ± 0.9 ml/min). Adenosine release during the second test was higher ($p < 0.05$) than in the first test (2.5 ± 0.5 vs. 3.9 ± 0.5 nmol/min at 3 min of the first and second tests, $p < 0.01$).**

Conclusions. **These results indicate that the warm-up phenomenon is not attributable to increased coronary flow but to attenuation of increased regional myocardial oxygen consumption, which may be mediated by adenosine A_1 receptor activation.**

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After a brief period of exercise-induced ischemia in patients with coronary artery disease, a warm-up phenomenon (1) occurs and the myocardium becomes more resistant to subsequent exercise. Studies (1–4) have shown a lengthening of exercise time and a decrease in severity of myocardial ischemia in the second exercise period. Jaffe and Quinn (2) observed a reduction in electrocardiographic (ECG) signs of myocardial ischemia in the second bicycle exercise test, an observation that agrees with the findings of MacAlpin and Kattus (3). Jaffe and Quinn (2) suggested coronary vasodilator effects rather than myocardial metabolic effects during the second exercise period as a possible mechanism of the warm-up phenomenon. Rizi et al. (4) also suggested that the increased tolerance to exercise is attributable not to decreased myocardial oxygen consumption but to decreased coronary vascular tone. In contrast, Williams et al. (5) showed that adaptation to tachycardia in patients with coronary artery disease during a second rapid pacing period was caused by a decrease in myocardial oxygen consumption rather than an increase in coronary blood flow. However, their observation does not necessarily reveal the precise mechanism of the warm-up phenomenon during exercise stress testing because systemic hemodynamic and neurohumoral factors, as well as local myocardial mechanical and metabolic variables, may differ in pacing and exercise stress tests. The hemodynamic and metabolic conditions before and during angina in patients with coronary artery disease are thought to be more closely reproduced in the exercise stress test than in the pacing stress test. Changes in local metabolic factors of the myocardium rather than systemic hemodynamic variables are suggested to account for the tolerance to ischemia (5). Adenosine is one substance that increases the tolerance (6–11). In experimental studies, increases in tolerance to ischemia and necrosis are reported to be attributable to endogenous adenosine (10), mainly through activation of adenosine A_1 receptors (11), possibly indicating that endogenous adenosine may be increased and thus attenuate myocardial oxygen consumption during the warm-up phenomenon.

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Table 1. Clinical and Angiographic Findings

Pt No.	Age (yr)/ Gender	Coronary Angiogram (% diameter reduction)				Left Ventricular Angiogram	
		LAD	LCx	RCA	Collateral Filling	EF (%)	Wall Motion
1	55/M	99	0	25	0	61	Normal
2	48/M	95	0	0	0	68	Normal
3	57/F	99	0	0	1	62	Normal
4	57/M	95	0	0	0	48	Ant. hypokinesia
5	63/M	99	0	25	0	56	Ant. hypokinesia
6	64/F	95	0	25	0	50	Normal
7	46/M	99	25	50	1	63	Normal
8	45/M	99	50	25	0	66	Normal
9	58/F	99	25	25	1	52	Ant. hypokinesia
10	62/M	95	0	25	0	64	Normal
11	48/M	95	0	0	0	60	Normal
12	60/M	99	25	25	0	64	Normal
13	44/F	95	0	0	0	55	Normal

Ant = anterior; EF = ejection fraction; F = female; LAD = left anterior descending coronary artery; LCx = left circumflex artery; M = male; RCA = right coronary artery.

Thus, in the present study, patients with effort angina underwent two consecutive exercise tests to determine whether reduction of myocardial oxygen consumption or an increase in coronary blood flow is responsible for the warm-up phenomenon. In addition, plasma adenosine concentration was measured to examine whether the release of adenosine is enhanced in the second exercise test.

Methods

Study patients (Table 1). The study group comprised 13 patients (9 men and 4 women with a mean age of 54 years [range 44 to 64]) who had coronary artery disease and a history of stable exertional angina pectoris. Patients were selected on a consecutive basis when the following inclusion criteria were fulfilled: 1) a history of stable effort-related angina pectoris; 2) coronary angiographic documentation of >90% stenosis (diameter reduction) of the proximal left anterior descending coronary artery; 3) absence of stenosis >50% of the left main, circumflex or right coronary artery; 4) presence of conditions that made it possible to catheterize the great cardiac vein with a thermodilution catheter and to easily sample the blood from this vein; and 5) presence of sinus rhythm. No patient had ST segment elevation during dynamic exercise or a history of angina pectoris at rest. All patients underwent an upright bicycle exercise test before catheterization while receiving their usual medical regimen. Sublingual nitroglycerin was allowed for treatment of an anginal attack, but all other cardiac medications were discontinued for at least 24 h before the study. Patients with a history of angina at rest or clinical evidence of old myocardial infarction were excluded. No attempt was made to obtain a history of the warm-up phenomenon from these patients before their recruitment.

Collateral filling was examined according to the scale proposed by Rentrop and colleagues (12): 0 = no visible filling by collateral channels, 1 = collateral filling of branches of the stenotic vessel with no filling of the epicardial segment of this vessel, 2 = partial collateral filling of the epicardial segment of the stenotic vessel, and 3 = complete collateral filling of the stenotic vessel.

Cardiac catheterization. Patients underwent right and left heart catheterization in the fasting state. Written informed consent was obtained from all patients. Premedication consisted of hydroxyzine, 50 mg, administered intramuscularly 15 min before catheterization. A no. 7F or 8F coronary sinus flow catheter (Wilton-Webster) was advanced under fluoroscopic guidance into the great cardiac vein (13), and great cardiac vein flow (ml/min) was measured by the thermodilution method. The catheter tip was positioned at the junction of the anterior interventricular and the great cardiac veins. Coronary venous drainage at this site is reported to originate mainly from the myocardium in the distribution of the left anterior descending coronary artery (14). Coronary venous angiograms were recorded on a video disk recorder, and the position of the catheter tip was confirmed to be stable at the time of each blood sampling and flow measurement by repeated fluoroscopy. Aortic pressure was measured with a Judkins catheter introduced through the right or left brachial artery. Pulmonary artery and right atrial pressure and cardiac output were measured with a Swan-Ganz thermodilution catheter.

Blood sampling. Simultaneous paired blood samples were obtained from the great cardiac vein and aorta to determine the oxygen saturation and adenosine concentration. The plasma after centrifugation was packed in dry ice for later determination of the norepinephrine concentration. Blood gases were measured with the ABL Radiometer (ABL-2, Copenhagen Apparatus). Coronary arteriovenous oxygen difference was assessed by the differences between coronary artery and vein oxygen saturation. Regional myocardial oxygen consumption was calculated by multiply-

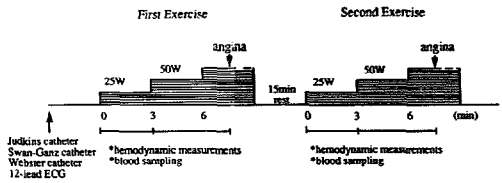


Figure 1. Schematic diagram of the exercise protocol. The second exercise test was performed 15 min after the first. Each patient began exercise at a work load of 25 W (150 kiloponumeters/min). The work load was increased every 3 min by increments of 25 W. ECG = electrocardiogram.

ing great cardiac vein flow (ml/min) by the coronary arteriovenous oxygen difference.

Adenosine measurement. The methods of adenosine measurement have been reported previously (15,16). Briefly, 1 ml of blood was drawn into a syringe containing 0.5 ml of dipyridamole (0.02%) and 100 μl of 2′-deoxycoformycin (0.1 mg/ml) with 20 μl ethylenediaminetetraacetic acid (EDTA) (500 mmol/liter) to block the uptake of adenosine by red blood cells and degradation of adenosine. After centrifugation, the supernatant was obtained and radioimmunoassay methods for analyzing adenosine content were employed. Adenosine in the plasma (100 μl) was succinylated by 100 μl of dioxane containing succinic acid anhydride and triethylamine. After a 10-min incubation, the mixture was diluted with 800 μl of 0.3 mol/liter imidazole buffer (pH 6.5). The assay mixture contained 100 μl of sample, 100 μl of succinyl [^{3}H]-adenosine (25,000 counts/min in 1 pmol), and 100 μl of diluted antiadenosine serum. After the mixture had been kept in an ice-cold water bath for 24 h, a cool suspension of dextran-coated charcoal (500 μl) was added. The charcoal was centrifuged, and 0.5 ml of the supernatant was counted for radioactivity in a liquid scintillation counter. The amount of adenosine degradation during the blood sampling procedure and the degradation rate of adenosine were reported to be negligible (15,16).

Norepinephrine measurements. The method of norepinephrine measurement has been described previously (17). Five milliliters of arterial blood taken into a tube containing EDTA was immediately placed in ice water and centrifuged for 20 min. Plasma norepinephrine was adsorbed on alumina and separated by high performance liquid chromatography (pump, LC-3A; column Zpax-SCX; Shimazu Seisakusho). Plasma norepinephrine was determined spectrofluorometrically by the trihydroxyindole method (Shimazu spectrofluorophotometer RF-500LCA).

Exercise protocol. The study protocol comprised two successive bicycle ergometer exercise tests performed in the supine position (Fig. 1). The second exercise test was performed 15 min after the first test. Each patient began exercise at a work load of 25 W (150 kilopond-meters/min) that was increased every 3 min in stepwise increments of 25 W. For all patients, the exercise was discontinued when anginal pain occurred. Hemodynamic variables were measured every minute. Great cardiac vein flow was recorded, and blood from the great cardiac vein and aorta were simultaneously sampled to determine regional myocardial oxygen consumption at rest, at the end of each stage of work load and at maximal exercise. A standard 12-lead ECG was recorded at rest and during exercise. The ECG data were compared at the same exercise time and at equivalent work loads. The sequence of each measurement at each stage of the work load was as follows: First, blood in the great cardiac vein and aorta was simultaneously sampled at 3 min of exercise and at the onset of angina while cardiac output was measured simultaneously by the Swan-Ganz thermodilution catheter. After sampling, which was performed within 10 s, coronary venous flow was measured within 20 s. Therefore, these procedures for blood sampling and hemodynamic measurements were performed within 30 s. The identical sequence of measurement of hemodynamic variables and blood sampling was used throughout the study.

Statistical analysis. Hemodynamic and metabolic variables at rest and during exercise were compared between the first and second exercise tests using a paired Student *t* test. Simple linear regression was used for correlation coefficients to compare the reduction in regional myocardial oxygen consumption at 3 min of exercise and the increase in maximal exercise time. Two-way analysis of variance with repeated measures was used to test the difference of responses of each variable during the first and second exercise tests. All values were expressed as mean value ± SE, and $p < 0.05$ was considered statistically significant.

Results

The hemodynamic and angiographic studies were completed without complications (Table 1). The mean exercise time to the onset of angina was significantly ($p < 0.01$) longer (507 ± 44 s) during the second than during the first exercise test (410 ± 42 s) (Table 2). The ECG showed a significantly lesser extent of ST segment depression at the time of onset of effort angina during the second than during the first exercise test (1.1 ± 0.2 mm vs. 1.7 ± 0.2 mm, $p < 0.01$). These results indicate that a warm-up phenomenon, that is, lengthening of exercise time and attenuation of ischemia, is observed in the second exercise test.

Systemic hemodynamics. Systemic hemodynamic data—heart rate, mean aortic pressure, pulmonary artery end-

Table 2. Exercise Duration and Changes in Systemic Hemodynamics During the First and Second Exercises

Pt No.	Exercise Duration (s)	HR (beats/min)			mAoP (mm Hg)			SI (ml/m²)			PAEDP (mm Hg)			RPP (×100)		
		R	3 min	A	R	3 min	A	R	3 min	A	R	3 min	A	R	3 min	A
First Exercise Test																
1	250	60	87	95	110	120	124	40	43	46	8	20	22	85	132	155
2	240	56	84	94	102	116	120	55	56	54	7	14	17	74	124	141
3	345	74	94	105	100	105	121	40	50	54	6	18	20	101	143	172
4	680	68	86	116	99	100	118	48	49	39	6	7	10	87	112	179
5	520	62	86	110	92	111	134	42	50	46	5	12	22	86	131	184
6	250	78	94	98	88	98	102	57	59	59	8	14	17	87	118	129
7	650	76	92	115	98	104	124	58	60	50	7	10	14	92	121	186
8	550	56	74	80	118	120	141	39	39	51	7	16	23	78	113	143
9	250	61	61	119	113	124	126	46	62	71	5	13	18	94	149	182
10	400	77	98	114	110	118	126	42	51	58	9	15	19	112	151	182
11	400	64	91	126	110	116	127	47	54	58	5	11	18	95	145	212
12	380	100	119	122	110	120	128	43	51	75	10	15	18	151	184	216
13	420	64	88	108	90	93	114	46	41	52	6	9	13	86	116	187
Mean	410	69	89	108	103	111	123	46	51	55	7	13	18	94	134	174
± SE	42	3	4	4	3	3	3	2	2	3	0	1	1	5	6	7
Second Exercise Test																
1	300	64	88	98	106	126	135	42	47	51	9	18	21	90	134	163
2	310	61	82	99	105	110	122	57	53	48	7	16	21	79	118	168
3	390	74	92	109	102	104	125	40	45	50	8	15	20	105	138	180
4	750	68	88	114	104	108	120	47	43	43	6	7	10	88	118	180
5	600	60	86	108	100	115	130	41	50	46	6	11	22	84	139	186
6	380	75	92	100	87	100	106	53	59	60	9	14	17	83	121	140
7	720	82	98	124	96	100	110	49	55	48	6	7	12	98	118	184
8	680	61	75	89	111	118	148	34	37	49	9	14	21	84	112	162
9	305	68	96	125	103	124	134	51	62	56	4	7	19	90	158	218
10	585	69	94	127	109	110	120	51	62	56	11	13	20	99	139	211
11	510	72	87	122	114	112	125	47	58	57	5	7	19	101	125	181
12	560	105	114	130	128	119	120	41	56	50	12	16	20	164	166	198
13	500	63	95	115	88	94	112	46	57	65	5	7	11	72	124	177
Mean	507	71	91	112	104	111	124	46	53	52	7	12	18	95	132	181
± SE	44	3	3	4	3	3	3	2	2	2	1	1	1	6	5	6
p value*	< 0.01	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	< 0.05

*p values comparing first and second exercise tests. 3 min = at 3 min of exercise; A = at the onset of angina; HR = heart rate; mAoP = mean aortic pressure; PAEDP = pulmonary artery end-diastolic pressure; R = at rest; RPP = rate-pressure product; SI = stroke index.

diastolic pressure and stroke index in the basal state at 3 min of exercise and at maximal exercise are shown in Table 2. There were no significant differences between these variables in the first and second exercise tests in the basal state, at 3 min after the onset of exercise or at maximal exercise.

Coronary hemodynamics. Great cardiac vein flow and the calculated coronary artery resistance in the basal state, at 3 min of exercise and at maximal exercise are shown in Table 3. There were no significant differences between the first and second exercise tests in changes in great cardiac vein flow and coronary artery resistance during each condition.

Regional myocardial oxygen consumption. No significant differences in basal regional myocardial oxygen consumption were observed between exercise tests (Table 3). Although the same exercise work load was imposed at 3 min of each exercise, the increases in regional myocardial oxygen consumption were lower in the second than in the first exercise test ($p < 0.01$) (Table 3). When an anginal attack was apparent at the maximal work load, the increases in oxygen consumption were comparable. There was a significant correlation between the extent of reduction in regional myocardial oxygen consumption at 3 min of exercise and the increase in maximal exercise time (Fig. 2).

Adenosine release during exercise. Adenosine release into the great cardiac vein was significantly greater in the basal state, at 3 min and at maximal exercise in the second than in the first exercise test (Table 3, Fig. 3). The increases in adenosine release during 0 to 3 min in the first exercise test were larger ($p < 0.05$) than in the second test.

Plasma norepinephrine levels during exercise. The plasma norepinephrine concentration in the blood of the aorta increased during both the first and the second exercise tests (Table 3). There were no significant differences in the extent of this increase.

Table 3. Changes in Coronary Hemodynamic and Metabolic Responses During the First and Second Exercise Tests

Pt No.	Exercise Duration (s)	GCVF (ml/min)			CAR (mmHg/ml per min)			MVO2 (ml/min)			Adenosine (pmol/ml) Aorta			Adenosine (pmol/ml) GCV			Norepinephrine (ng/ml)		
		R	3 min	A	R	3 min	A	R	3 min	A	R	3 min	A	R	3 min	A	R	3 min	A
First Exercise Test																			
1	250	32	60	80	3.4	2.0	1.6	3.3	6.6	8.9	12.8	13.8	14.9	31.1	35.2	39.5	—	—	—
2	240	95	120	145	1.1	1.0	0.8	7.8	10.7	13.3	39.2	42.3	61.3	52.1	62.3	120.1	—	—	—
3	345	78	137	174	1.3	0.8	0.7	6.8	12.4	16.5	14.9	16.8	17.8	31.2	52.3	78.1	—	—	—
4	680	56	69	80	1.8	1.4	1.3	6.0	8.0	9.9	6.5	6.8	9.6	25.0	27.8	31.4	0.30	0.51	1.24
5	520	38	50	72	2.3	2.2	1.9	3.6	5.0	7.3	12.3	11.2	11.3	47.8	62.3	78.1	0.28	0.32	0.36
6	250	42	60	68	2.1	1.6	1.5	4.2	6.6	7.6	7.5	7.6	9.0	28.6	36.5	54.6	0.37	0.52	0.80
7	650	50	90	197	2.1	1.2	0.6	5.6	10.6	23.1	26.8	28.9	30.6	37.9	44.1	52.0	0.07	0.17	0.28
8	550	95	128	191	1.2	0.9	0.7	10.2	14.2	21.7	21.6	21.9	31.9	49.9	53.9	122.7	0.14	0.19	0.29
9	250	34	41	48	3.3	3.0	2.6	3.7	4.4	5.3	—	—	—	—	—	—	—	—	—
10	400	61	90	105	1.8	1.3	1.2	6.9	10.4	12.1	—	—	—	—	—	—	—	—	—
11	400	48	70	126	2.3	1.7	1.0	4.4	6.5	12.1	—	—	—	—	—	—	—	—	—
12	380	62	94	115	2.0	1.3	1.1	7.3	11.4	14.5	—	—	—	—	—	—	—	—	—
13	420	45	60	97	2.0	1.6	1.2	4.3	6.4	10.7	—	—	—	—	—	—	—	—	—
Mean	410	57	82	115	2.1	1.5	1.3	5.7	8.7	12.5	17.7	18.7	23.3	38.0	46.8	72.1	0.23	0.34	0.59
± SE	42	6	9	14	0.2	0.2	0.2	0.6	0.9	1.5	3.9	4.3	6.3	3.8	4.6	12.2	0.06	0.08	0.19
Second Exercise Test																			
1	300	34	54	82	3.1	2.3	1.6	3.5	5.7	9.3	9.8	12.9	14.9	42.8	55.6	58.9	—	—	—
2	310	92	112	150	1.1	1.0	0.8	7.3	9.6	13.7	33.7	42.1	51.3	63.2	87.9	130.3	—	—	—
3	390	80	138	178	1.3	0.8	0.7	7.1	12.3	16.7	10.5	16.5	16.8	47.9	57.5	99.1	—	—	—
4	750	52	70	86	2.0	1.5	1.4	5.3	7.6	10.2	10.3	11.8	12.8	34.2	51.4	69.8	0.30	0.31	1.31
5	600	37	51	70	2.7	2.3	1.9	3.3	4.9	6.8	12.9	13.1	12.1	61.3	73.9	91.8	0.27	0.44	0.47
6	380	41	58	70	2.1	1.7	1.5	4.1	6.1	7.7	7.8	9.2	10.3	32.6	48.2	68.3	0.30	0.36	0.60
7	720	56	88	200	1.7	1.1	0.6	6.2	9.8	23.8	20.1	31.6	28.3	66.1	77.0	90.3	0.14	0.18	0.27
8	680	93	120	208	1.2	1.0	0.7	9.6	13.1	24.1	17.2	16.3	31.7	57.2	63.9	155.2	0.14	0.16	0.41
9	305	30	40	48	3.4	3.1	2.8	3.1	4.2	5.6	—	—	—	—	—	—	—	—	—
10	585	52	76	111	2.1	1.4	1.1	5.9	8.6	13.1	—	—	—	—	—	—	—	—	—
11	510	51	63	103	2.2	1.8	1.2	4.8	5.8	9.9	—	—	—	—	—	—	—	—	—
12	560	66	82	100	1.9	1.5	1.2	7.8	9.7	12.3	—	—	—	—	—	—	—	—	—
13	500	49	60	90	1.8	1.6	1.2	4.9	6.1	9.8	—	—	—	—	—	—	—	—	—
Mean	507	56	78	115	2.0	1.6	1.3	5.6	8.0	12.5	15.3	19.2	22.3	50.7	64.4	95.5	0.23	0.29	0.61
± SE	44	6	8	14	0.2	0.2	0.2	0.5	0.8	1.6	3.0	4.1	3.0	4.7	4.9	11.6	0.04	0.05	0.18
p value	< 0.01	NS	< 0.01	NS	NS	< 0.01	NS	NS	< 0.01	NS	NS	NS	NS	< 0.01	< 0.01	< 0.01	NS	NS	NS

CAR = coronary artery resistance; GCV = great cardiac vein; GCVF = great cardiac vein flow; MVO2 = regional myocardial oxygen consumption; other abbreviations as in Table 2.

Discussion

We demonstrated in the present study that 1) the warm-up phenomenon is attributable to reduction of regional myocardial oxygen consumption rather than to increases in great cardiac vein flow in the second exercise test, 2) this reduction in regional myocardial oxygen consumption is not caused by changes in the systemic hemodynamic variables, and 3) adenosine release during the second exercise test is greater than that during the first test.

Reduction of myocardial oxygen consumption as the major cause of the warm-up phenomenon. Several investigators (2–4) have suggested that increased coronary vasodilation during exercise may increase the tolerance to ischemia in patients with angina pectoris; however, no direct evidence that supports this idea has been presented. Gage et al. (18) demonstrated that active vasomotion of stenotic coronary arteries during dynamic exercise in patients with angina pectoris may affect exercise time. This observation agrees with the finding of Rizi et al. (4), who showed that the exercise tolerance to ischemia may be due to changes in coronary vascular tone. However, because all of our patients had severe concentric and organic stenosis, the coronary vasomotion of the stenotic arteries might not be changed when the warm-up phenomenon was observed. Indeed, the extent of increases in the great cardiac vein flow did not change during the first and second exercise tests, suggesting that the warm-up phenomenon was not due to changes in coronary vascular tone. However, great cardiac vein flow may not necessarily reflect myocardial perfusion of the area supplied by the left anterior descending coronary artery (19). Several investigators, using the canine experimental model, reported that 70% to 90% of the myocardial

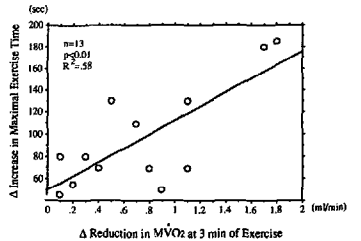
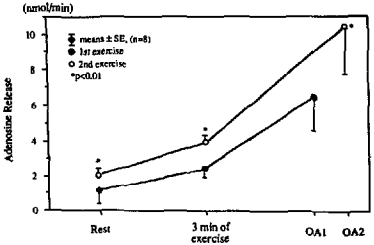


Figure 2. Correlation between the extent of the reduction in regional myocardial oxygen consumption ($M\dot{V}O_2$) at 3 min of exercise and the increase in maximal exercise time. The reduction in myocardial oxygen consumption at 3 min of exercise correlated well with the prolonged exercise time ($p < 0.01$).

perfusion may reflect great cardiac vein flow (19). This difference, if it exists, would not affect our observation because the value of great cardiac vein flow was larger in the first than in the second exercise test (82 ± 9 vs. 78 ± 8 ml/min). Nevertheless, intramyocardial flow distribution might be improved in the second exercise test even when great cardiac vein flow is identical in the two tests. We cannot exclude this possibility because improvements in intramyocardial flow distribution, that is, an increase in endocardial flow at the expense of epicardial flow, may attenuate the severity of ischemia (20). This improved flow distribution is thought to improve myocardial contraction and increase myocardial oxygen consumption. However, the present study demonstrated that myocardial oxygen consumption is reduced during the second exercise test, suggesting that this reduction, independent of the increase in myocardial perfusion in the second exercise, contributes to the mechanism of the warm-up phenomenon.

Figure 3. Changes in adenosine release during two consecutive exercise tests. The **horizontal axis** shows the levels at rest, at 3 min of exercise and at the onset of angina. Adenosine release was significantly higher during the second than during the first exercise test at all points. The responses in adenosine release in the first and second exercise tests are significantly ($p < 0.05$) different. OA1 = onset of angina during the first exercise test; OA2 = onset of angina during the second exercise test.



The reduction in myocardial oxygen consumption in the second exercise test was observed only during exercise, not in the basal state. This observation suggests that changes in myocardial mechanical and metabolic properties, such as myocardial stunning and hibernation due to transient ischemia, may not be involved in the warm-up phenomenon. If contractile dysfunction were the cause of the reduced myocardial oxygen consumption, this reduction would probably be observed in the basal state. Because baseline myocardial oxygen consumption did not differ between the first and second exercise tests, the contractile dysfunction after the first exercise test may not account for the ischemic tolerance in the second test. Nevertheless, we cannot exclude this possibility because we did not observe regional wall motion in the present study. Rather, these observations suggest that release of humoral factors exerting a negative inotropism is augmented only during the second exercise test and that these factors may suppress the increases in the myocardial oxygen consumption.

Enhanced adenosine release as a possible underlying mechanism of the warm-up phenomenon. Adenosine release was greater during the second than during the first exercise test. This observation raises the question of which effects of adenosine are attributable to the increase in the exercise time and the attenuation of the severity of ischemia in the patients with coronary artery disease. Although adenosine potently increases coronary blood flow (9,15,21), our study revealed that coronary vasodilation is not the cause of the warm-up phenomenon. The absence of coronary vasodilation, even with enhanced release of adenosine during the second exercise test, may be due to the existence of severe coronary stenosis. One possible explanation is that coronary resistance vessels in such patients are considerably relaxed to maintain adequate coronary flow even in the baseline state. Thus, additional increases in adenosine release may minimally contribute to further coronary vasodilation during the second test. The second possibility is that coronary vascular vasodilator capability is reduced at the second exercise test because of transient ischemia in the first test. Indeed, it has been reported that a brief period of ischemia reduces coronary vasodilator capacity (22). The third possibility is that coronary vasodilation during exercise may be attributable not to adenosine but to the other factors, such as partial pressures of oxygen and of carbon dioxide, catecholamines or endothelium-derived relaxing factor. In contrast, the effects of adenosine on the attenuation of myocardial contractility enhanced by norepinephrine may not be exhausted because norepinephrine and adenosine levels in blood of the systemic circulation were not high enough to saturate myocardial contractile effects of both substances. Adenosine affects myocardial contractility only when it is

enhanced by beta-adrenergic stimulation, but it does not affect the basal myocardial contractility and oxygen consumption (23–26). Furthermore, adenosine is reported to inhibit norepinephrine release from the presynaptic nerve endings (27–29), which may attenuate increases in myocardial oxygen consumption during exercise.

These lines of evidence agree with the idea that enhanced adenosine release during the second exercise period may be one cause of the warm-up phenomenon. However, we could not clarify this relation because we could not test whether this phenomenon is abolished by an adenosine receptor antagonist. At present, only theophylline and aminophylline are available for clinical use as adenosine receptor antagonists. However, they are less potent for antagonizing adenosine receptors than is 8-phenyltheophylline or 8-sulfophenyltheophylline, and they also have other cardioprotective effects, such as inhibition of phosphodiesterase, increases in cyclic adenosine monophosphate and stimulation of alpha$_1$-adrenoceptors. These other effects make it difficult to determine the cause and effect relation even when theophylline or aminophylline is used in the second exercise test. Therefore, at present we have no tool for proving a cause and effect relation between the increased release of adenosine and the warm-up phenomenon in clinical settings.

Another question is what mechanism is at work in the enhanced release of adenosine in the second exercise test. One possibility is that the basal levels of adenosine are elevated during the second exercise test simply because of the aftereffects of ischemia. The values of adenosine release in the basal state were higher in the second than in the first exercise test. This offset level of adenosine may simply increase the release of adenosine in the second test. In the dog model, a higher level of adenosine was found to continue for at least 10 to 15 min after a brief period of ischemia (30). Another possibility is that norepinephrine released during the first exercise test potentiates the adenosine production through activation of alpha$_1$-adrenoceptors and, thereby, of protein kinase C. It is reported that adenosine production in hypoxic rat cardiomyocytes is enhanced by activation of protein kinase C. Protein kinase C may activate the 5′-nucleotidase responsible for the adenosine production (31). The first exercise may increase 5′-adenosine monophosphate, a substrate of 5′-nucleotidase, for adenosine production. However, we have no direct or indirect evidence to prove these hypotheses.

Limitations of the present study. Several investigators (32,33) have suggested that changes may occur in the position of the catheter used to measure the great cardiac vein flow and to sample the blood from the great cardiac vein, increasing the variability among repeated measurements of the flow and blood sampling. However, Magorien et al. (34) found a highly significant correlation between these two measurements during exercise. We confirmed that the position of the catheter did not change when blood sampling and measurements of the great cardiac vein flow were performed. Furthermore, for the measurements of the great cardiac vein flow we obtained a thermodilution curve on a multichannel recorder to confirm that the curve obtained was of regular form. Irregular curves are thought to be caused by contamination with right atrial blood.

The degradation of adenosine is thought to be very rapid. To minimize the degradation, we sampled the blood with a syringe containing stop solution. The sampling time was 10 s for all patients. Although some of the adenosine may have been degraded during this sampling period, the sampling times for the first and second exercise tests were comparable because the flow rate of the great cardiac vein was comparable. These results support the finding that release of adenosine is enhanced in the second exercise test because the ratio of the degraded adenosine should have been the same for samples from the first and second tests, although the absolute value of adenosine release from the myocardium may have been higher than the observed values.

Clinical implications. Recently much attention has been focused on ischemic preconditioning because this procedure dramatically attenuates the size of the infarcted myocardium (10,11). Our study indicates that the preceding ischemic episode increases adenosine production and attenuates the severity of ischemia. Because adenosine is also reported to limit infarct size (8), its enhanced release after ischemic preconditioning may attenuate infarct size. Also, potentiation of adenosine production in the ischemic myocardium, such as by 5-amino-4-imidazole carboxamide riboside (35), may help reduce the ischemia and the infarct size, although further investigation is necessary to validate the beneficial effects of adenosine in clinical settings.

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